2015-03

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Morrison, VL

10.1016/j.jval.2014.12.013
Value in Health
Elsevier BV

VALUE IN HEALTH 18 (2015) 206–216

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/jval

Patient-Reported Outcomes

Predictors of Self-Reported Adherence to Antihypertensive Medicines: A Multinational, Cross-Sectional Survey

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ABSTRACT

Background: Nonadherence to antihypertensive medicines limits their effectiveness, increases the risk of adverse health outcome, and is associated with significant health care costs. The multiple causes of nonadherence differ both within and between patients and are influenced by patients' care settings. **Objectives:** The objective of this article was to identify determinants of patient nonadherence to antihypertensive medicines, drawing from psychosocial and economic models of behavior. **Methods:** Outpatients with hypertension from Austria, Belgium, England, Germany, Greece, Hungary, The Netherlands, Poland, and Wales were recruited to a cross-sectional online survey. Nonadherence to medicines was assessed using the Morisky Medication Adherence Scale (primary outcome) and the Medication Adherence Rating Scale. Associations with adherence and nonadherence were tested for demographic, clinical, and psychosocial factors. **Results:** A total of 2595 patients completed the questionnaire. The percentage of patients classed as nonadherent ranged from 24% in The Netherlands to 70% in Hungary. Low age, low self-efficacy, and respondents' perceptions of their illness and cost-related barriers were associated with nonadherence measured on the Morisky Medication Adherence Scale across several countries. In multilevel, multivariate analysis, low self-efficacy (odds ratio = 0.73; 95% confidence interval 0.70–0.77) and a high number of perceived barriers to taking medicines (odds ratio = 1.70; 95% confidence interval 1.38–2.09) were the main significant determinants of nonadherence. Country differences explained 11% of the variance in nonadherence. **Conclusions:** Among the variables measured, patients' adherence to antihypertensive medicines is influenced primarily by their self-efficacy, illness beliefs, and perceived barriers. These should be targets for interventions for improving adherence, as should an appreciation of differences among the countries in which they are being delivered.

Keywords: adherence, behavioral economics, health psychology, hypertension, self-efficacy.

Introduction

Adherence to antihypertensive treatments is suboptimal [1], even among patients participating in clinical studies, whose median persistence with medicines is only about 1 year [2]. Patients who are poorly adherent (proportion of days covered ≤40%) [3] experience significantly increased risk of acute cardiovascular events, compared with those who adhere adequately (≥80%), and incur greater health care costs [4]. The World Health Organization [5] has called for further research to gain a better understanding of the determinants of nonadherence to antihypertensive medicines, and to identify common risk factors for nonadherence across different countries, to inform strategies for improving patient adherence.

Known determinants of nonadherence to antihypertensive treatments may broadly be categorized as factors related to the patients [6–9] and their familial and cultural context [10], condition [11], treatment [8,11], socioeconomic characteristics, and health professional/health care system [5,12]. Components of sociocognitive and self-regulatory theory including attitude [13], perceived behavioral control [13,14], low self-efficacy [13,15,16], lack of perceived treatment benefits [11], perceived barriers [7,8], illness perceptions [6,10], beliefs about medicines [6,11,17,18], and lack of social support [10,19,20] are significantly associated with

Conflict of interest: V.L.M., E.A.F.H., S.P., C.O.P., W.C., S.D.G., F.D., P.K., and D.A.H. indicate that they have no competing interests to disclose. B.V. is an employee of the AARDEX Group, a MWV Healthcare Company.

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http://dx.doi.org/10.1016/j.jval.2014.12.013

nonadherence. Studies based on the consumer demand theory support the negative impact of the costs of medicines on adherence [21], but there is a lack of empirical evidence on alternative behavioral economic theories such as time preference. We are unaware of any study in which a range of these factors has been tested simultaneously to assess their combined contribution to nonadherence across several countries.

The aim of this study, therefore, was to identify determinants of patient nonadherence to antihypertensive medicines, drawing from psychosocial and economic models of behavior, from a cross-sectional survey across a number of European countries with contrasting cultures, health care systems, and patient characteristics.

Methods

The research used an online, convenience cross-sectional sample of adults with hypertension recruited from 11 European countries. We tested the contribution of multiple, theory-driven determinants for association with antihypertensive treatment nonadherence, and reported our findings according to the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) statement on cross-sectional studies [22].

Procedure

After receipt of ethical approval from all relevant committees, we invited ambulatory, adult patients with hypertension to participate in an online questionnaire. Patients self-selected into this study in response to advertisements placed in community pharmacies (Austria, Belgium, England, France, Germany, Greece, The Netherlands, Portugal, Poland, and Wales) or hypertension clinics (Hungary). Additional strategies were necessary to increase recruitment in some countries. These included recruiting patients via general practice surgeries (Poland and Hungary), placing advertisements in the press (England and Wales), and using online patient support groups (Poland). No incentive was offered for patients to participate. The survey was administered anonymously through SurveyMonkey, with one entry allowed per Internet Protocol address to reduce the chance of multiple responses. Patient information sheets, consent forms, and eligibility checks were provided online.

Inclusion Criteria

We included patients who consented, and who self-reported as being 18 years or older, diagnosed by a doctor as having hypertension that lasted at least 3 months, currently prescribed antihypertensive medicine(s), and personally responsible for administering their medicines.

Exclusion Criteria

Respondents who self-reported as being diagnosed with a "psychiatric condition" or those living in a nursing home (or similar facility) were excluded.

Potential Determinants

Potential determinants of nonadherence were identified from published literature reviews [23,24]. The questionnaire was developed from validated instruments, where available, and covered participants' demographic characteristics, use of medicines, self-rated health [25], and a battery of scales derived from economic [21] and sociocognitive [23,24] theories.

Affordability and cost-related behaviors were assessed by a dichotomous question asking whether respondents had to think about the money available to spend when obtaining their medicines and six related items, each measured on a five-point Likert scale [26]. Components of the European Social Survey [27] assessed household income: participants reported their main source of income, their total annual income (in bands), whether they were coping with their present income, and the ease or difficulty in borrowing money when in need. We assessed participants' time preference for near versus distant enjoyment of health benefits [28]. The internationally standardized European Task Force on Patient Evaluations of General Practice (EUROPEP) measure [29] assessed participants' evaluations of the health care they receive.

Validated, self-report tools were used to assess personal and sociocognitive determinants of nonadherence. Dispositional optimism was measured using the Life Orientation Test on five-point Likert scales [30]. Illness representations were measured using the Brief Illness Perception Questionnaire [31], which assessed personal beliefs about illness consequence, timeline, personal control, treatment control, illness identity, concern about illness, illness coherence, and emotional representations (the causal subscale was removed because of translation issues). The Beliefs about Medicines Questionnaire [32] assessed participants' belief in the necessity of their medicines and also concerns about their medicines. Components of the theory of planned behavior [33,34] measured attitudes/behaviors toward taking medicines, subjective norms of adherence, barriers to, and facilitators of, adherence, intention to adhere, and self-efficacy for adherence behaviors, each scored on a five-point Likert scale. The Building Research Initiative Group Illness Management and Adherence in Transplantation (BRIGHT) questionnaire [35,36] was used to assess constraints/facilitators of adherence using subscales for barriers and social support.

Outcome Measures

The primary outcome measure was self-reported nonadherence, based on the four-item Morisky Medication Adherence Scale [37]. This classified patients as being nonadherent according to a single "yes" response to any of the four questions that made specific reference to "high blood pressure medicine." This validated scale is the most frequently used questionnaire measuring adherence to medication [38]. An exploratory analysis was also conducted of those categorized as intentionally nonadherent on the basis of "yes" responses to two specific Morisky items that identify nonadherence as a result of feeling better/worse. A secondary outcome measure of adherence was provided by the Medication Adherence Rating Scale (MARS) [39], which consisted of five items rated on a Likert scale, with a low score (on a range of 5–25) indicating lower levels of adherence. Our choice of outcome measures was informed by the theoretical and empirical literature on medication adherence spanning the behavioral and medical sciences from which the study questions emerged. These two conceptually different measures provided dichotomous data on nonadherence and continuous data on adherence to patients' antihypertensive medications.

The final survey had a total of 135 items.

Translation

Measures that were not validated and available in the required language were translated into the appropriate languages using accredited translators who were native speakers of the target languages and fluent in English. Translations were checked for compatibility with the original version in a process of back translation, performed by persons who were native English speakers and fluent in each target language, to ensure that none of the original meaning was lost. For each language, a third individual acted as a reviewer and highlighted any discrepancies between the forward and back translations, which were resolved by discussion with the translators. All translations were

Table 1 – Demographic data and cross-country comparison.

Explanatory variable	Country (no. of respondents)									χ^2 *P* value
	Austria (323)	Belgium (180)	England (323)	Germany (274)	Greece (289)	Hungary (323)	The Netherlands (237)	Poland (323)	Wales (323)	
Age, mean (95% CI)	60.2 (58.8–61.5)	57.3 (55.6–59.1)	59.6 (58.5–60.7)	56.8 (55.4–58.2)	63.9 (62.6–65.2)	58.2 (56.8–59.7)	58.3 (57.0–59.5)	54.5 (53.2–55.8)	61.1 (59.9–62.2)	16.62 $P < 0.001$ $df = 8$
Sex: female	145 (44.9)	64 (35.6)	141 (43.7)	154 (56.2)	173 (59.9)	179 (55.4)	115 (48.5)	171 (52.9)	119 (36.8)	64.54 $P < 0.001$ $df = 8$
Education										
Secondary only*	120 (37.2)	6 (3.3)	110 (34.1)	51 (18.6)	148 (51.2)	253 (78.3)	7 (3.0)	167 (51.7)	98 (30.3)	64.54 $P < 0.001$ $df = 8$
Higher education	194 (60.1)	174 (96.7)	211 (65.3)	222 (81.0)	135 (46.7)	68 (21.1)	229 (96.6)	155 (48.0)	224 (69.3)	
Marital status: married	209 (64.7)	134 (74.4)	241 (74.6)	184 (67.2)	187 (64.7)	234 (72.4)	186 (78.5)	246 (76.2)	258 (79.9)	36.11 $P < 0.001$ $df = 8$
Student/in employment	119 (36.8)	98 (54.4)	166 (51.4)	150 (54.7)	119 (41.2)	124 (38.4)	151 (63.7)	169 (52.3)	143 (44.3)	70.47 $P < 0.001$ $df = 8$
Health status										
Poor	23 (7.1)	4 (2.2)	10 (3.1)	6 (2.2)	0 (0)	26 (8.0)	5 (2.1)	24 (7.4)	13 (4.0)	322.59 $P < 0.001$
Fair	96 (29.7)	25 (13.9)	53 (16.4)	84 (30.7)	93 (32.2)	128 (39.6)	49 (20.7)	133 (41.2)	51 (15.8)	$df = 24$
Good	128 (39.6)	77 (42.8)	123 (38.1)	140 (51.1)	140 (48.4)	132 (40.9)	112 (47.3)	138 (42.7)	116 (35.9)	
Very good	74 (22.9)	72 (40.0)	137 (42.4)	44 (16.1)	55 (19.0)	36 (11.1)	69 (29.1)	28 (8.6)	142 (44.0)	
Mean number of medical conditions (95% CI)	2.84 (2.59–3.08)	2.29 (2.10–2.47)	2.28 (2.15–2.42)	2.13 (1.97–2.30)	2.85 (2.64–3.06)	2.85 (2.68–3.02)	2.08 (1.93–2.24)	2.15 (2.02–2.27)	2.42 (2.26–2.57)	13.16 $P < 0.001 df = 8$
Mean number of medicines (95% CI)	4.43 (4.06–4.79)	3.54 (3.19–3.90)	3.84 (3.58–4.10)	3.42 (3.14–3.70)	4.37 (3.99–4.75)	5.17 (4.80–5.53)	3.44 (3.09–3.79)	4.12 (3.83–4.42)	3.80 (3.54–4.06)	12.01 $P < 0.001$ $df = 8$
Mean units of medicines per day (95% CI)	5.51 (4.95–6.07)	3.78 (3.33–4.23)	4.93 (4.45–5.40)	3.92 (3.56–4.27)	5.06 (4.57–5.54)	7.44 (6.90–7.98)	4.31 (3.45–5.16)	3.20 (2.89–3.51)	4.97 (4.45–5.49)	22.41 $P < 0.001$ $df = 8$
Most frequently dosed medicine										
Once daily	114 (35.3)	123 (68.3)	224 (9.3)	100 (36.5)	51 (17.6)	54 (16.7)	157 (66.2)	131 (40.6)	241 (74.6)	557.56 $P < 0.001$
Twice daily	110 (34.1)	35 (19.4)	63 (19.5)	129 (47.1)	112 (38.8)	155 (48.0)	56 (23.6)	143 (44.3)	47 (14.6)	$df = 16$
≥Thrice daily	96 (29.7)	19 (10.6)	26 (8.0)	44 (16.1)	123 (42.6)	113 (35.0)	22 (9.3)	48 (14.9)	35 (10.8)	

Note. Data are counts (%), unless otherwise indicated.

CI, confidence interval.

* Secondary education meaning to secondary (high) school level.

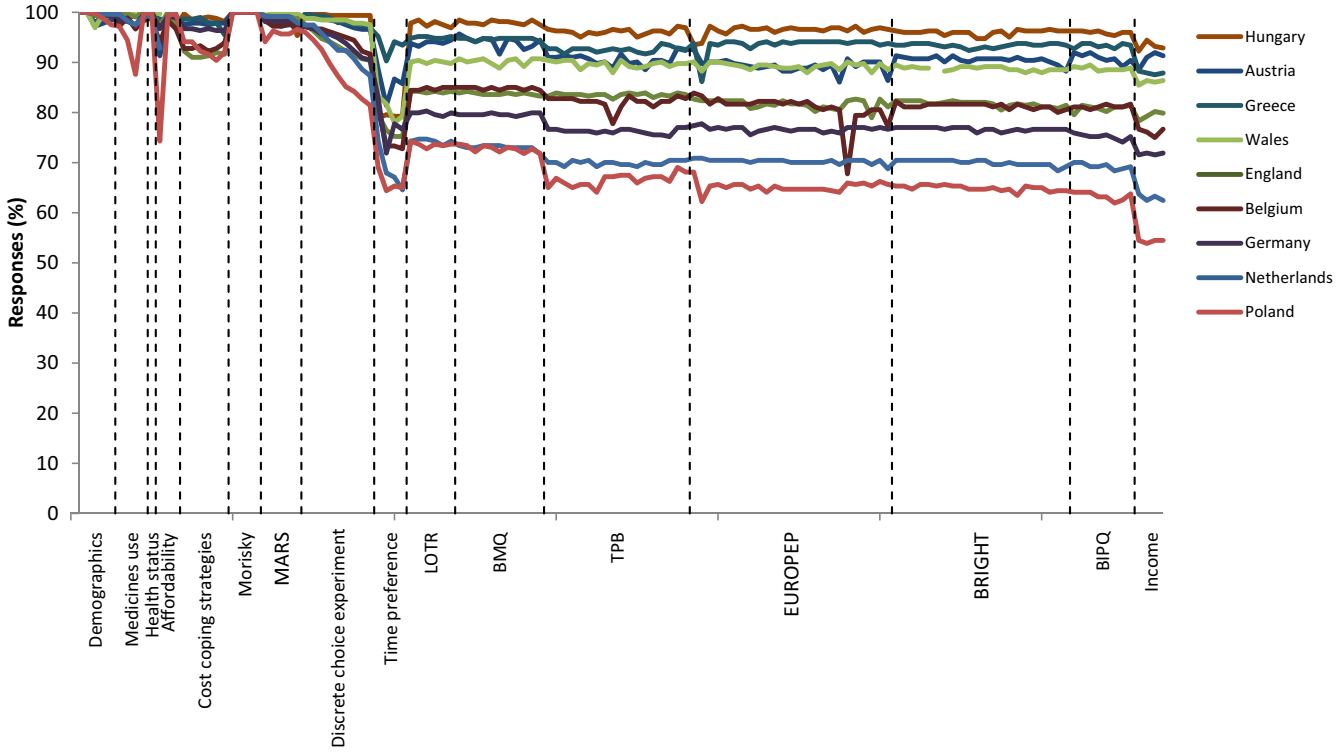

Fig. 1 – Percentage of complete responses according to country and item of the questionnaire. BIPQ, Brief Illness Perception Questionnaire; BMQ, Beliefs about Medicines Questionnaire; BRIGHT, Building Research Initiative Group Illness Management and Adherence in Transplantation; EUROPEP, European Task Force on Patient Evaluations of General Practice; LOTR, Life Orientation Test Revised; MARS, Medication Adherence Rating Scale; TPB, theory of planned behavior.

coordinated by one project partner to ensure consistency. Piloting in each country enabled identification of any semantic inconsistencies.

Sample Size

Based on an expectation of 30% nonadherence [6] and a one-sided 5% level of significance, 323 completed Morisky scores were required per country for within-country analyses.

Data Analysis

Responses to the survey were coded in SPSS (version 19; IBM Corporation, Armonk, NY) and analyzed in Stata (version 10; StataCorp LP, College Station, TX). We assumed missing data to be missing at random and imputed using multiple imputations by chained equations [40], to create 25 data sets for each country. For a single incomplete variable, multiple imputation constructs a model relating the incomplete variable to variables in the prediction model, and draws from the posterior predictive distribution of the missing data, conditional on the observed data. Using multiple imputations by chained equations, imputed values were initialized by drawing at random from observed values. Imputation of missing data was performed on variables ordered by level of "missingness," using observed and current imputed values of all predictors. To ensure stability, this imputation step was cycled 10 times for each of the 25 imputed data sets [41]. Analyses were performed on each set, and imputation-specific coefficients were pooled according to Rubin's rules [42]. Imputed data were used for all analyses with the exception of demographic variables for which data from complete cases were used.

In the primary analysis, we calculated the percentage of patients classed as nonadherent according to the Morisky score in each country. Potential associations with nonadherence were initially tested univariately using chi-square and independent samples t tests (associations with the use of medicines were adjusted for age), followed by a logistic regression with nonadherence as the dependent variable. We applied a bivariate method of selecting explanatory variables, whereby only variables found to be significant ($P < 0.05$) in the univariate analysis were entered into the regression model based on a theoretical order [43,44], from determinants classified as demographic and medicine use characteristics (distal) to attitudes and behaviors (proximal). Assumptions regarding multicollinearity, singularity, normality, linearity, and homoscedasticity were tested and met. Country comparison analysis was conducted using chi-square tests. We adopted a similar approach for the secondary outcome of MARS adherence, but with a one-way analysis of variance to test differences among countries.

To account for both within-country and between-country variance, as a secondary analysis, two-level multilevel regression models with respondents nested within country were specified for both Morisky (logit model) total and intentional nonadherence, and MARS adherence (linear regression model). Multilevel models with random intercepts and fixed effects were specified, initially with all variables common to all countries. Noncontributory variables were subsequently removed iteratively, determined by highest P value using backwards elimination (based on $P > 0.05$). We calculated the variance partition coefficient [45] to determine the attribution of country to the observed variance in nonadherence.

A complete case analysis of Morisky total nonadherence was performed to assess the sensitivity of our main findings to

Table 2 – Prevalence of self-reported total nonadherence and intentional nonadherence across European countries based on Morisky responses, and adherence based on MARS.

Country	Morisky		MARS
	Respondents self-reporting as being nonadherent (as a percentage of all respondents) (95% CI)	Respondents self-reporting as being intentionally nonadherent (as a percentage of nonadherers) (95% CI)	Mean score (95% CI)*
The Netherlands	24.1 (18.6–29.5)	21.1 (10.5–31.6)	23.86 (23.64–24.16)
Germany	33.2 (27.6–38.8)	35.2 (25.4–45.0)	23.47 (23.28–23.75)
Austria	33.7 (28.6–38.9)	51.4 (42.0–60.8)	23.25 (23.03–23.56)
Wales	38.1 (32.8–43.4)	25.2 (17.5–32.9)	23.46 (23.30–23.77)
Belgium	38.9 (31.8–46.0)	17.1 (8.3–26.0)	23.59 (23.50–23.99)
England	41.5 (36.1–46.9)	23.9 (16.7–31.1)	23.41 (23.17–23.65)
Greece	50.2 (44.4–55.9)	57.2 (49.2–65.3)	22.08 (21.71–22.48)
Poland	57.6 (52.2–63.0)	44.6 (37.5–51.8)	18.19 (17.77–19.01)
Hungary	70.3 (65.3–75.3)	18.1 (13.1–23.1)	22.88 (22.74–23.26)
Cross-country comparison	χ^2: 191.52 *df*: 8 $P = 0.000$ Tests cross-country difference in self-reported nonadherence	χ^2: 108.87 *df*: 8 $P = 0.000$ Tests cross-country difference in self-reported intentional nonadherence, as a proportion of all self-reported nonadherence	ANOVA *F* test: 106.08–115.49† (Complete case *F*: 103.24) $P = 0.000$

CI, confidence interval; MARS, Medication Adherence Rating Scale.
* 95% CI of mean based on imputed data.
† Range of imputation-specific statistics.

assumptions relating to missing data. In a post hoc analysis, we assessed the impact of excluding Hungary from the analysis, given that Hungary alone recruited patients from hypertension clinics.

Results

Participants

A total of 2630 adults from 11 countries completed the questionnaire. Target recruitment was achieved in five countries (Austria, England, Hungary, Poland, and Wales). Study setup and initiation was delayed in Belgium, Germany, Greece, and The Netherlands, leading to nontarget recruitment. The analysis, therefore, includes these countries that each recruited more than 100 participants (n = 2595). There was an inadequate level of available research support in France and Portugal that resulted in low response (n = 11 and n = 33, respectively), and these were excluded from the analysis. Included participants' characteristics are presented in Table 1. The overall level of missing data by country ranged from 5% to 26%, with lowest rates seen on demographic and clinical questions (0%–8%), MARS (<2%), medicine necessity and concerns (14%), and self-efficacy (14%) and highest rates seen on the income questions (22%), time preference (22%), and BRIGHT barriers (23%) (Fig. 1).

There were significant differences between country samples on all demographic and clinical characteristics assessed. Self-rated health was more often rated as poor or fair in Poland (48.6%) and Hungary (47.6%) than in Belgium (16.1%), England (19.5%), and Wales (19.8%). Fewer respondents from Hungary, Greece, and Poland had received higher education than in other countries. Respondents from Greece tended to be older and more predominantly female, and together with Hungary and Austria had the greatest number of comorbidities and were more likely to be taking medicines more frequently than three times a day.

Prevalence of Nonadherence

Based on Morisky scores, it was found that nonadherence was least prevalent in The Netherlands and most prevalent in Hungary (Table 2). Intentional nonadherence was highest in Greece. Polish respondents had significantly lower levels of adherence, as measured by MARS, than did respondents from other countries.

Associations with Morisky Nonadherence and MARS Adherence

Among demographic factors, only age showed associations across several countries, with younger age associated with Morisky nonadherence in Austria, Belgium, The Netherlands, and Wales (Table 3) and older age associated with MARS adherence in The Netherlands (Table 4). Unemployment was associated with nonadherence in England and Hungary only. None of the medicine-related factors showed associations with nonadherence in more than one country. The perceived ease or difficulty in borrowing money was associated with nonadherence in England and Germany, and having available strategies to cope with the costs of medicines was significantly associated with MARS-rated adherence in Belgium, England, Greece, and Hungary.

No significant associations were evident for optimism, but, in contrast, beliefs about the illness did play a significant role. Brief Illness Perception Questionnaire factors of low perceived illness consequences, low concern about illness, and low beliefs in personal control over illness were significantly associated with nonadherence on the Morisky scale in Austria, Greece, Poland, and Wales (Table 3), and high belief in treatment control, high

Table 3 – Summary of the logistic regression model using the Morisky nonadherence as the dependent variable[*].

Explanatory variable[†]	Country								
	Austria	Belgium	England	Germany	Greece	Hungary	The Netherlands	Poland	Wales
Demographic characteristics									
Age	0.96 (0.93– 0.99) $P = 0.012$	0.97 (0.95– 1.00) $P = 0.047$	0.98 (0.94–1.03) $P = 0.431$	0.97 (0.94–1.01) $P = 0.012$			0.94 (0.91–0.98) $P = 0.001$	0.98 (0.94–1.00) $P = 0.088$	0.97 (0.93–1.00) $P = 0.037$
Employment	1.32 (0.56– 3.13) $P = 0.521$		3.14 (1.34–7.34) $P = 0.008$	1.25 (0.49–3.19) $P = 0.646$		2.93 (1.58–5.42) $P = 0.001$		1.12 (0.55–2.27) $P = 0.762$	0.82 (0.37–1.82) $P = 0.618$
Sociodemographic characteristics/clinical factors									
Number of tablets	0.97 (0.88–1.07) $P = 0.502$				0.88 (0.78–0.98) $P = 0.025$				
Dosing frequency									
Once daily				0.08 (0.03–0.26) $P < 0.001$					
Twice daily				0.24 (0.09–0.62) $P = 0.004$					
Income source	0.72 (0.31– 1.67) $P = 0.445$		0.99 (0.36–2.73) $P = 0.977$	3.83 (1.31–11.18) $P = 0.014$					1.08 (0.45–2.58) $P = 0.864$
Borrowing income									
Difficult			6.26 (1.14–34.46) $P = 0.035$		3.01 (0.81–11.12) $P = 0.098$	1.30 (0.64–2.62) $P = 0.469$			
Neither difficult nor easy			5.28 (0.93–30.17) $P = 0.061$		1.82 (0.43–7.72) $P = 0.418$	3.36 (1.34–8.43) $P = 0.010$			
Easy			5.47 (1.00–29.77) $P = 0.050$		3.08 (0.65–14.59) $P = 0.157$	0.59 (0.24–1.47) $P = 0.261$			
Number of items prescribed	1.06 (0.95–1.19) $P = 0.313$		0.86 (0.76–0.97) $P = 0.017$	0.84 (0.70–1.00) $P = 0.051$					
Illness perceptions									
Illness consequences	0.89 (0.81– 0.99) $P = 0.029$								
Personal control	0.94 (0.84– 1.04) $P = 0.230$		0.94 (0.83–1.07) $P = 0.333$		0.79 (0.66–0.95) $P = 0.013$	0.93 (0.82–1.06) $P = 0.289$			0.88 (0.79–0.99) 0.031
Concern about illness								0.79 (0.68–0.92) $P = 0.002$	
Theory of planned behavior									
Barrier					1.28 (1.03–1.60) $P = 0.028$		1.26 (0.97–1.63) $P = 0.078$		0.93 (0.72–1.22) $P = 0.610$
Self-efficacy	0.79 (0.70– 0.90) $P < 0.001$	0.82 (0.69–0.96) $P = 0.016$	0.62 (0.52–0.74) $P < 0.001$	0.53 (0.43–0.67) $P < 0.001$	0.82 (0.71–0.95) $P = 0.006$	0.84 (0.73–0.96) $P = 0.013$	0.81 (0.68–1.04) $P = 0.111$	0.70 (0.60–0.82) $P < 0.001$	0.66 (0.56–0.79) $P < 0.001$
BRIGHT									
Barriers	1.04 (1.00–1.08) $P = 0.035$		1.04 (0.98–1.10) $P = 0.155$		1.05 (1.00–1.10) $P = 0.061$	1.05 (1.00–1.10) $P = 0.051$		1.06 (1.00–1.11) $P = 0.034$	1.05 (0.99–1.11) $P = 0.107$
Constant[‡]	133.99 (6.92–2593.41) $P = 0.001$	33.32 (4.06–273.37) $P = 0.001$	11.78 (0.17–833.40) $P = 0.256$	649.33 (28.07–15018.96) $P < 0.001$	8.10 (0.36–183.93) $P = 0.189$	4.13 (0.49–35.10) $P = 0.194$	33.71 (1.92–591.49) $P = 0.016$	320.84 (9.36–10993.92) $P = 0.001$	124.91 (1.44–10848.02) $P = 0.034$

continued on next page

Table 3 – *continued*

Explanatory variable†	Country								
	Austria	Belgium	England	Germany	Greece	Hungary	The Netherlands	Poland	Wales
Other predictors in the model where $P > 0.05$§	2, 18, 19, 22, 24	20	6, 7, 8, 9, 15, 16, 17, 19, 20, 25		1, 9, 10, 13, 15, 17, 19, 20, 25	9, 10, 17, 23, 26	11, 12	10, 13, 14, 15, 16, 22, 25	3, 4, 5, 15, 17, 20, 21, 23, 25
Final model χ^2 and P value‖	64.94, 78.87 $P < 0.001$	14.36, 27.28 $P < 0.001$	104.25, 145.31 $P < 0.001$	89.41, 123.04 $P < 0.001$	76.51, 89.42 $P < 0.001$	64.02, 81.23 $P < 0.001$	25.74, 47.98 $P < 0.001$	76.56, 120.57 $P < 0.001$	75.19, 94.15 $P < 0.001$

BRIGHT, Building Research Initiative Group Illness Management and Adherence in Transplantation; CI, confidence interval.

* Figures are reported as odds ratio (95% CI) and exact P values.

† Only odds ratios for predictors with $P < 0.05$ for at least one country are presented.

‡ Constant reported for all values of P.

§ Number of medical conditions (1), number of different medicines (2), income deciles 1 to 4 (3), income deciles 5 to 7 (4), income deciles 8 to 10 (5), perception of income: living comfortably (6), perception of income: coping (7), perception of income: finding it difficult (8), affordability problem (9), cost-coping strategies (10), time preference: long (11), time preference: short (12), prescriber of medicines (13), sex of prescriber (14), satisfaction with practitioner (15), satisfaction with practice (16), optimism (17), timeline (18), treatment control (19), illness coherence (20), emotional representations (21), necessity of medicines (22), concern about medicine (23), attitude (24), intention (25), social support (26).

‖ Because χ^2 cannot be pooled, we report the range of imputation-specific χ^2. The degrees of freedom per imputation are given by (number of variables − 1). Imputation-specific P values were $P < 0.001$ in all cases, with the exception of three imputations in Belgium (which were $P = 0.001$, 0.001, 0.002).

illness coherence, and high belief in personal control were significant in Austria, Greece, and Hungary based on MARS assessment of adherence (Table 4). Illness identity, perceived illness timeline, and emotional representations were not significant, neither were beliefs about medicines, in terms of their necessity or concerns about taking them (Beliefs about Medicines Questionnaire).

The sociocognitive variables, drawn mainly from the theory of planned behavior, did not emerge consistently in the intercountry analysis. Perceived barriers to adherence (whether changes to daily routine makes taking medicines more difficult) were related to nonadherence only in Greece, although a high number of barriers assessed by BRIGHT [35,36] were associated with nonadherence in Austria and Poland. Intention to adhere was associated with adherence in Hungary and Wales. Low self-efficacy, however, emerged significant in relation to nonadherence in all countries except The Netherlands, and high self-efficacy explained adherence in all countries except Poland. Social support factors emerged significant only in Hungary but in a counterintuitive direction, in relation to low perceived environmental support and greater adherence.

The variables examined in this study explained between 13.4% and 65.2% of the variability in MARS adherence (Table 4).

Multilevel Model

The multilevel logit model for Morisky nonadherence identified males, being of younger age, being employed, low number of medicines, high dosing frequency, high normative beliefs, low self-efficacy, high perceived barriers, low personal control, low concern about illness, and difficulty in borrowing money as being significantly associated with nonadherence (Table 5). Associations were consistent in the model specified with Morisky *intentional* nonadherence. Multilevel linear regression found that older age, a lower level of education, a greater number of medicines, less frequent dosing, having low perceived barriers, low perceptions of illness consequences, beliefs in treatment control, and high self-efficacy were connected to higher adherence as measured by MARS. Based on the Morisky scale, 11% and 7% of the explained variance in total and intentional nonadherence, respectively, was attributable to differences among countries and 23% of the variance in adherence based on MARS was attributable to differences among countries.

Sensitivity Analysis

The analysis of complete cases resulted in less precise estimators, as expected, altering the significance of some variables and hence their inclusion in the final model. Self-efficacy and perceived barriers (BRIGHT), however, remained significant as in the primary analysis.

When Hungary was excluded from the multilevel model (because of the aforementioned difference in recruitment method), we observed a reduction in between-country variance in Morisky nonadherence (from 11% to 4%). Other factors emerged as being significant, including education, number of medical conditions, attitudes, and intention to adhere, though self-efficacy and barriers remained significant.

Discussion

Self-reported nonadherence to antihypertensive medicines is prevalent, even among the sampled population who were in receipt of a current prescription for antihypertensive treatment. Prevalence differs significantly across countries, and although a proportion of this variance is explained by country-level effects and demographic characteristics, our principal finding is that

Table 4 – Summary of the final regression model (all variables) using the MARS adherence-dependent variable: β coefficient (95% CIs).

Explanatory variable*	Country								
	Austria	Belgium	England	Germany	Greece	Hungary	The Netherlands	Poland	Wales
Demographic characteristics									
Age	0.01 (−0.02 to 0.03) $P = 0.606$	0.00 (−0.02 to 0.03) $P = 0.922$	0.02 (−0.01 to 0.05) $P = 0.109$	0.02 (−0.01 to 0.04) $P = 0.153$			0.03 (0.00–0.06) $P = 0.026$		0.00 (−0.02 to 0.03) $P = 0.976$
Sex				0.39 (−0.10 to 0.88) $P = 0.119$					0.49 (0.00–0.98) $P = 0.050$
Sociodemographic/clinical factors									
Cost-coping strategies	−0.10 (−0.22 to 0.01) $P = 0.076$	−0.17 (−0.30 to −0.06) $P = 0.004$	−0.12 (−0.21 to −0.02) $P = 0.020$	−0.06 (−0.16 to 0.05) $P = 0.319$	−0.35 (−0.42 to −0.28) $P < 0.001$	−0.21 (−0.28 to −0.15) $P < 0.001$		−0.12 (−0.25 to 0.02) $P = 0.094$	
Time preference									
Short					7.12 (2.14–12.09) $P = 0.005$				
Illness perceptions									
Personal control			0.01 (−0.10 to 0.11) $P = 0.931$		−0.11 (−0.26 to 0.04) $P = 0.144$	0.17 (0.04– 0.30) $P = 0.011$	0.11 (−0.02 to 0.24) $P = 0.102$	0.05 (−0.24 to 0.33) $P = 0.735$	0.05 (−0.05 to 0.15) $P = 0.348$
Treatment control	0.26 (0.13–0.39) $P < 0.001$		0.13 (−0.02 to 0.28) $P = 0.095$	−0.02 (−0.17 to 0.13) $P = 0.794$	0.08 (−0.08 to 0.24) $P = 0.299$	−0.09 (−0.25 to 0.07) $P = 0.284$		0.11 (−0.27 to 0.50) $P = 0.558$	0.07 (−0.08 to 0.20) $P = 0.366$
Illness coherence			−0.07 (−0.20 to 0.06) $P = 0.274$		0.17 (0.02– 0.32) $P = 0.032$	0.08 (−0.06 to 0.21) $P = 0.257$			−0.01 (−0.13 to 0.10) $P = 0.814$
Theory of planned behavior									
Intention	−0.09 (−0.25 to 0.07) $P = 0.286$		0.06 (−0.17 to 0.28) $P = 0.623$		0.15 (−0.03 to 0.33) $P = 0.112$	0.32 (0.09– 0.55) $P = 0.007$		−0.01 (−0.53 to 0.51) $P = 0.971$	0.33 (0.04–0.62) $P = 0.028$
Self-efficacy	0.28 (0.16–0.40) $P < 0.001$	0.19 (0.02–0.36) $P = 0.027$	0.30 (0.17–0.42) $P < 0.001$	0.32 (0.19–0.46) $P < 0.001$	0.39 (0.26– 0.52) $P < 0.001$	0.15 (0.03– 0.26) $P = 0.016$	0.25 (0.09–0.41) $P = 0.002$	0.29 (−0.03 to 0.61) $P = 0.072$	0.37 (0.22–0.51) $P < 0.001$
BRIGHT									
Barriers	−0.04 (−0.07 to 0.00) $P = 0.062$	−0.01 (−0.05 to 0.03) $P = 0.698$	−0.04 (−0.09 to 0.01) $P = 0.081$	−0.00 (−0.03 to 0.03) $P = 0.893$	−0.05 (−0.09 to 0.01) $P = 0.010$	−0.07 (−0.11 to −0.03) $P = 0.101$		−0.08 (−0.17 to 0.00) $P = 0.057$	−0.06 (−0.11 to 0.00) $P = 0.060$
Social support	−0.02 (−0.09 to 0.04) $P = 0.520$		0.00 (−0.04 to 0.05) $P = 0.920$			−0.05 (−0.10 to −0.01) $P = 0.024$			0.03 (−0.02 to 0.07) $P = 0.270$
Constant	18.97 (15.83–22.10) $P < 0.001$	21.72 (19.04–24.40) $P < 0.001$	17.83 (13.96– 21.69) $P < 0.001$	20.15 (17.35–22.96) $P < 0.001$	19.06 (16.32–21.80) $P < 0.001$	19.76 (16.70– 22.82) $P < 0.001$	19.48 (17.29–21.68) $P < 0.001$	13.74 (8.97–18.51) $P < 0.001$	19.37 (15.86– 22.88) $P < 0.001$
Other predictors in the model where $P > 0.05$[†]	2, 6, 11, 13, 14, 20, 22, 23	11, 14, 20	3, 8, 9, 10, 11, 13, 14, 15, 16, 17, 18, 19, 20, 22, 24	13, 14, 16, 17, 19, 20, 22	3, 5, 7, 8, 10, 11, 12, 14, 15, 17, 19, 24	1, 7, 10, 13, 14, 15, 16, 17, 19, 20, 22, 23, 24	24	13, 21, 23	3, 4, 5, 8, 11, 13, 14, 15, 16, 17, 19, 20, 23, 24
Adjusted R^2	0.2831	0.2005	0.3809	0.2223	0.6521	0.4589	0.1335	0.1482	0.3570

BRIGHT, Building Research Initiative Group Illness Management and Adherence in Transplantation; MARS, Medication Adherence Rating Scale.

* Only coefficients for predictors with $P < 0.05$ for at least one country are presented.

† Marital status (1), employment (2), dosage frequency (3), number of medicines (4), number of medical conditions (5), income source (6), total income (7), income perception (8), borrowing (9), affordability problem (10), health status (11), time preference: long (12), satisfaction with practitioner (13), satisfaction with practice (14), optimism (15), illness consequences (16), identity (17), concern about illness (18), emotional representations (19), concern about medicine (20), necessity of medicine (21), attitude (22), normative beliefs (23), barriers—theory of planned behavior (24).

Table 5 – Summary of multilevel regression models for Morisky and MARS as outcome measures.

Explanatory variable	Morisky		MARS	
	Odds ratio	95% CI	β coefficient	95% CI
Sex	1.22*	1.01–1.47		
Age	0.98†	0.97–0.99	0.01*	0.00–0.02
Employment	0.74*	0.59–0.94		
Education			−0.34‡	−0.60 to −0.09
Number of medicines	0.89†	0.86–0.93	0.06*	0.01–0.10
Dosing frequency	1.30‡	1.12–1.52	−0.24‡	−0.42 to −0.06
Normative beliefs	1.05*	1.01–1.09		
Self-efficacy	0.73†	0.70–0.77	0.36†	0.30–0.42
Barriers (BRIGHT)	1.70†	1.38–2.09	−0.83†	−1.10 to −0.57
Illness consequences			−0.06*	−0.10 to −0.01
Personal control	0.94‡	0.90–0.97		
Treatment control			0.11‡	0.04–0.19
Concern about illness	0.94‡	0.91–0.98		
Borrowing money	0.85‡	0.78–0.94		
Constant	34.59†	13.5–88.5	19.45†	18.1–20.8
Random effects parameters	**Variance**	**95% CI**	**Variance**	**95% CI**
Between-country variance (σ_u^2)	0.40	0.15–1.07	2.14	0.79–5.80
Within-country variance (σ_e^2)			7.09	6.63–7.57
% variance attributable to differences between countries	10.82	4.35–24.49	23.20	10.63–43.40

Notes. For the logit model, $\sigma_e^2 = \pi^2/3$.
Variance partition coefficient = $\sigma_u^2/(\sigma_u^2 + \sigma_e^2)$.
Full model specification: age, sex, education, marital status, employment, number of medical conditions, number of different medicines, number of tablets, dosing frequency, number of items prescribed, health status, affordability problem, optimism, necessities, concerns about medicine, attitudes, normative beliefs, barrier (theory of planned behavior), facilitators, intention, self-efficacy, prescriber of medicines, sex of prescriber, satisfaction with practitioner, satisfaction with practice, barriers (averaged as one less collected in Wales), social support, illness consequences, illness timeline, personal control, treatment control, illness symptomaticity, concern about illness, illness coherence, emotional representations, income source, income perception, ease of borrowing, total income.
BRIGHT, Building Research Initiative Group Illness Management and Adherence in Transplantation; CI, confidence interval; MARS, Medication Adherence Rating Scale.
* $P < 0.05$.
† $P < 0.001$.
‡ $P < 0.01$.

potentially modifiable factors of low perceived self-efficacy and, to a lesser extent, low personal control beliefs and high perceived barriers are consistently associated with nonadherence. Perceived barriers to adherence included forgetfulness or interruption of daily routine, practical difficulties, and feeling overwhelmed by circumstances or complexity of regimen. Our finding of common associations with nonadherence across different countries supports the importance of these factors, particularly given the significant differences that exist in cultural, medical practices, and health care systems that contribute to a small proportion of the variance in nonadherence.

Adherence is generally explained by the converse of the above, but cost-related behavior (i.e., strategies to cope with the cost of prescriptions) and intention also emerged as significant in several countries. The multilevel analysis of all countries shows that although many factors act in the opposite direction depending on whether we are addressing nonadherence or adherence, some uniquely explain nonadherence, for example, employment status, low normative beliefs, low personal control, low illness concern, and low borrowing potential, and others uniquely explain adherence, for example, lower education, low perceived illness consequences (both these are counterintuitive), and beliefs in treatment control. The multilevel analyses also suggest that where possible, a reduction in dose frequency and number of prescribed medicines might achieve improvements in adherence.

The literature on adherence to medicines contains many analyses that have tested the significance of clinical, treatment, and demographic characteristics as predictors of nonadherence, assuming that behavior is a function of these characteristics alone. This approach has significant limitations. Our analysis is rooted in behavioral theories to reflect the notion that individual beliefs and social influences are potentially more relevant determinants of intentional and nonintentional nonadherence (and of adherence) than relatively fixed attributes of the person or the clinical situation. Previous studies have shown that, based on sociocognitive and self-regulation theories, personal and perceived control [6,10,13,15,16], perceived benefits of treatment [7,11], and perceived barriers—such as forgetfulness and experienced or anticipated adverse effects [7,8]—are significant predictors of nonadherence in patients taking antihypertensive medicines. Associations between higher levels of self-efficacy and adherence in patients with hypertension have been noted previously [13,46].

The novelty and key strength of our study is that a range of theoretically informed factors derived from behavioral theories in health psychology and economics were tested concurrently across several European countries. Our analysis also considered the distinction between intentional and unintentional nonadherence. Associations with intentional nonadherence were fewer, and although several overlapped with those associated

with overall nonadherence, that is, age, self-efficacy, and perceived barriers, other factors included the number of medical conditions, concerns about medicines, perceived illness identity, and behavioral intention. The act of deliberately choosing to avoid taking medicines, therefore, warrants interventions that more explicitly target illness and treatment and behavioral beliefs.

There are several caveats to our analysis, however, which may limit the strength of the interpretations. First, only 5 of the intended 11 countries reached target recruitment. We pragmatically included all nine countries that recruited an appreciable number of patients; however, this reduced the precision of the estimates of nonadherence in each country and limited the strength of inferences. Second, our analyses might be confounded by differences in methods of recruitment. Although all countries—except Hungary—recruited via community pharmacies, the exclusion of Hungary from the secondary analysis resulted in more variables being significant. The main findings of the primary (per country) analysis, however, remained unchanged. Third, because responses were elicited via self-administered questionnaires, we had no means of confirming hypertension diagnosis, nor other responses, or mitigate any self-presentation bias, which would reduce the external validity of our findings. Fourth, we were unable to assess the impact of nonresponse bias [47] because those who failed to complete the outcome measures—which were at the beginning of the questionnaire—were not allowed to progress through the remainder of the survey. The length of the survey represents a fifth limitation, which may have had an impact on completion rates. The variables ultimately emerging as being associated with nonadherence and adherence (i.e., theory of planned behavior barriers and self-efficacy), however, had relatively low levels of missingness and we improved precision by performing multiple imputation. Although multiple imputation addresses problems in complete case analyses related to loss of efficiency and bias due to differences between observed and unobserved data, it is no substitute for a complete data set and requires an important but unverifiable assumption that data are missing at random. Moreover, only subscale totals rather than every individual item were imputed for health psychology measures. This may introduce bias because data from respondents who completed some, but not all, of the items in a subscale were discarded. Sixth, although we used validated scales wherever possible, full testing of the BRIGHT measure did not exist at the time of the study. Finally, self-reported measures of adherence are prone to bias [38], and may not distinguish among failure to initiate dosing, incorrect implementation of the dosing regimen, and treatment discontinuation [48]. In mitigation, however, we used two measures of adherence and both had a significant association with self-efficacy.

Notwithstanding these limitations, the findings can inform the development of nonadherence-reducing (or adherence-enhancing) interventions. Most importantly, the common variables identified within our study are amenable to change through improved communication with health care professionals or brief cognitive-behavioral intervention. Reviews of adherence-improving interventions [49,50] offer support for self-efficacy enhancement, with modest effects reported in trials of supportive and individually tailored telephone calls, information on self-management, checks on understanding, and concerns regarding medicines and empowerment. Our analysis suggests that a theoretically informed, controlled trial of cognitive-behavioral interventions, focused on increasing self-efficacy and related control beliefs and reducing perceived barriers to adherence behaviors, is warranted. Given the broad spectrum of potential barriers and the observation of independent, country-level differences, which may be related to cultural, health service, or other factors, interventions that are tailored specifically to the population in which they are being delivered are the most likely to be effective.

Acknowledgments

We thank collaborators within participating countries for assistance with patient recruitment.

Source of financial support: This work was supported by the European Union's Seventh Framework Programme FP7/2007-2013 "Ascertaining Barriers to Compliance (ABC) project" (grant no. 223477). The funder had no role in the study design; in the collection, analysis, and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.

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